Draft Guidance for Industry: *Best Practices in Developing Proprietary Names for Drugs*

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Learning Objectives

- Understand the purpose of the *draft* Guidance for Industry: *Best Practices in Developing Proprietary Names for Drugs*
- Understand FDA's thinking on how to develop proprietary names that do not cause or contribute to medication errors or misbranding of the drug.
- Understand FDA's process for reviewing proposed proprietary names

FDA Guidance

- Two guidances related to proprietary names:
  1. Best practices for Developing Proprietary Names for Drugs- *draft*
  2. Contents of a Complete Submission (final)
- A “draft guidance,” when finalized, represents the FDA’s current thinking on a topic.
- It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

Background

- Proprietary name is a critical element in use of drug products
- Proprietary names that are similar phonetically or in their spelling or orthographic appearance or are otherwise confusing or misleading, may lead to errors.
- Medication errors are a significant public health concern that account for an estimated 7,000 deaths annually in the United States.
- Focus of draft guidance is to develop and communicate to sponsors a systematic, standardized, and transparent approach to proprietary name evaluation

Draft Guidance for Industry: Best Practices for Developing Proprietary Names for Drugs

- Issued May 28, 2014.
  - Comment period currently open
- Joint Guidance with CBER
- Applies to Rx and OTC products
- Intended to help sponsors of drugs and biological products develop proprietary names that do not cause or contribute to medication errors or the misbranding of the drug

Contents of Best Practices for Developing Proprietary Names for Drugs

I. Prescreening proprietary name candidates
II. Other attributes that may be misleading or error prone
III. Misbranding review
IV. Methods for Evaluating LASA Safety of Proposed Proprietary Names
    I. Name Simulation Studies
    II. Identify names with Orthographic, spelling, and phonetic similarity.

I. Prescreening proprietary name candidates

I. Prescreen the Proposed Name

Things to avoid:

- Obvious similarity to other names
- Inclusion of medical/coined abbreviations
- Inclusion or reference to inert or inactive ingredients
- For combination drug products: avoid suggesting the name of one or more, but not all active ingredients
- Inclusion of USAN stem
- Using the same root name for a product that does not share at least one common active ingredient
- Reusing a proprietary name of a different discontinued drug product

I. Prescreening: Obvious similarity to other names

FDA considers a proposed proprietary name to be misleading if it may be confused with the proprietary name or the established name of a different drug or ingredient because of similar spelling or pronunciation (21 CFR 201.10(c)(5)).

I. Prescreening: Inclusion of medical/coined abbreviations

- Sponsors should avoid using abbreviations, symbols, and dose designations in the proprietary name in a manner which could be misleading or lead to error

- A list of potentially confusing abbreviation/symbols can be found in The Joint Commission's "Do Not Use" list or the Institute for Safe Medication Practices (ISMP) List of Error-Prone Abbreviations, Symbols, and Dose Designations.

I. Prescreening: Inert or inactive ingredients

Proprietary names should not incorporate any reference to an inert or inactive ingredient (21 CFR 201.10(c)(4)).

I. Prescreening: Name suggesting active ingredients

Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).

I. Prescreening: Inclusion of USAN stem

- Proprietary names should not incorporate United States Adopted Name (USAN) stems in the position that USAN designates for the stem
- USAN stems are intended to indicate a pharmacological or chemical trait of a drug
- Use of these stems, even when such use is consistent with the USAN meaning, may lead to an increased risk of medication errors
- Only allowed in rare circumstances when the proposed name includes a word that can only be spelled in the English language using a stem in the position designated by USAN

I. Prescreening: Same root name for different active ingredients

- The term **root proprietary name** refers to the portion of a proposed proprietary name, generally within a product line extension, that is or has already been marketed.

- Sponsors should not use the same proprietary name or the same **root proprietary name** for products that do not contain at least one common active ingredient contained in the original marketed product

I. Prescreening: Reusing a proprietary name

- Do not reuse a proprietary name of a discontinued product for different drug or biological product

- Proprietary names are used in prescribing for an extended period of time even after product discontinuation and in some cases this has lead to name confusion errors

- There is a strong risk that users may continue to associate the name with the original discontinued product

II. Misleading Nature or Error Potential of Other Nomenclature Attributes

II. Misleading Nature or Error Prone Attributes

- Inclusion of product-specific attributes
- Use of modifiers
- Brand name extension
- Dual proprietary name
- Drug names used outside the US
- Rx to OTC switch
- Avoid symbols; use words.
- Use of sponsor name in the proprietary name

II. Misleading or Error Prone Attributes: Inclusion of product-specific attributes

- Although not reason for FDA rejection, FDA recommends that sponsors avoid incorporating product-specific attributes in the name
- When used, should be consistent with the product and not pose risk of medication error
- Sponsor may wish to consider future changes (in dosage form or route, etc.) may render the original proprietary name inaccurate

II. Misleading or Error Prone Attributes: Use of modifiers

- Some proprietary names are constructed of a root proprietary name modified by added words or components, which are referred to as **modifiers**.
- Modifiers may be used to convey;
  - Distinguishing product characteristics,
  - Delivery Device component,
  - Some other aspect of the product (e.g. indication, formulation etc.)

II. Misleading or Error Prone Attributes: Use of modifiers

- Considerations when selecting a modifier;
  - Is there a need for modifier?
  - Does the modifier accurately describes the product characteristic it is intended for?
  - Is the modifier currently used in the marketplace
  - What is the intended meaning? Do you have data to support HCP understand this meaning?
  - What is your rationale for the placement in relation to the root proprietary name?
  - Risk associated if modifier is misinterpreted or omitted

II. Misleading or Error Prone Attributes: Brand name extension

- A concern when same root proprietary name is used for multiple products without modifiers that adequately differentiate among the products

- Brand name extensions are evaluated by FDA on a case-by-case basis, and some areas we consider are;
  - If products share at least one common active ingredient
  - If products are differentiated by labeling (carton and container)
  - If modifiers used are appropriate and effective at differentiating the product among members of the same product line

II. Misleading or Error Prone Attributes: Dual proprietary name

- Distinct proprietary names for products that contain the identical active ingredient(s) but may have different indications of use
- Safety risks may be introduced by using dual proprietary names;
  - Overdose or dose-related adverse reactions due to duplicate therapy
  - Missing a drug-drug interaction
- FDA evaluates these proposals on a case-by-case basis along with any associated labeling that might address these potential risks.

II. Misleading or Error Prone Attributes: Names outside U.S

- Wrong-drug medication errors have occurred when a proprietary name for a product marketed in the United States is identical, or virtually identical in spelling and pronunciation, to a foreign product containing an entirely different active ingredient marketed in a foreign country.
- As a best practice, we recommend that you avoid proposing a proprietary name that is identical or nearly identical to a foreign product that contains a different active ingredient.

II. Misleading or Error Prone Attributes: Rx to OTC switch

- FDA evaluates on a case-by-case basis when drug product is "switched" from prescription to over-the-counter (OTC) status, and we consider;
  - Is it a full switch (i.e., all indications, dosing, strengths are same)?
  - Is it a partial switch (i.e., prescription-only status still applies to some indications, dosages, or strengths)?
  - Does it contain a modifier to distinguish between the OTC and prescription products, or other OTC versions in the same product line
- The sponsor can propose a completely new proprietary name for the OTC product, whether the switch is full or partial.

II. Misleading or Error Prone Attributes: Use of Sponsor name

- Proprietary names should not incorporate the sponsor's name across multiple products

- This practice can result in creating multiple similar proprietary names, which might increase the risk of confusion across products

III. Misbranding Review

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- Suggestions that a drug is safer or more effective than has been demonstrated by appropriate scientific evidence
- A fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not

IV. Look-alike Sound-alike (LASA) Safety Review

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- Consider similarity in printing, writing, and speech
- Conduct name simulation studies (NSS)
- Search for similar names using FDA's Phonetic and Orthographic Computer Analysis (POCA) program
  - Determine similarity scores with other marketed names via POCA
  - Categorize as high, moderate, or low similarity based on match score
- Use checklists for the high, moderate, or low similarity to help determine whether the name is safe from a LASA perspective

Name Simulation Studies (NSS)

- Purpose is to test how subjects respond to a proposed proprietary name by asking them to use the name in simulated real-world use conditions.
- We recommend that name simulation study results should be analyzed carefully to identify potential errors

NSS Design: General Considerations

- Draft guidance provides a sample Simulation Study format that applicants may consider using
- The more closely and fully the simulation approximates real-world use conditions, the more valuable the results of the simulation testing.
  - Reflect the full range and variety of tasks involved in the prescribing, transcribing, dispensing, and administration of drugs
  - Simulate characteristics of real use, such as using ruled or unruled paper, prescription pads, computer order entry, and telephone orders to approximate actual communication methods
  - Present the proposed proprietary name with the corresponding product characteristics (e.g., strength, route, dosage, and frequency) that are likely to be communicated in actual use

NSS Design: Participants, Scenarios and tasks

- Represent different prescribing scenarios based on all of the potential prescribing conditions and/or settings of use for the proposed product
- We recommend that participants are:
  - Actively practicing healthcare professionals, such as prescribers, transcribers, pharmacists, or nurses who administer the products in the proposed use conditions for the product.
  - Represent the full range of people who may be involved in the medication use process.
  - Generally, we do not consider it necessary to include patients, unless the name study is for an OTC drug

Analyze Results of NSS

- Quantitative data
  - How many times a participant interpreted a prescription correctly/incorrectly
- Qualitative data
  - Any concerns raised by the participants
  - For the misinterpretations: how was the name misinterpreted
    - Other drug names may represent a safety concern

Integrate Results of NSS into Overall LASA Assessment

- We recommend that any findings suggesting names of concern should be analyzed further
  - Consider scoring the name pair using POCA
  - Then, use the appropriate checklists to determine the potential for error.

Identify Names with Orthographic, Spelling and Phonetic Similarity

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- FDA enters the proposed proprietary name into the FDA's Phonetic and Orthographic Computer Analysis (POCA) system and queries the name against drug reference databases
  - Drugs@FDA , RxNorm
  - FDA also searches an internal list of proposed names

POCA Results

- Search will provide three data sets: COMBINED orthographic and phonetic matches, phonetic matches, and orthographic matches.
- We recommend review the COMBINED orthographic and phonetic matches
  - POCA development and testing was performed using the COMBINED match group

Why POCA

POCA 101

- POCA is an analytic tool designed to help identify drug and biologic names and medical terminology that are phonetically and orthographically similar to one another.

- POCA uses algorithms to assign similarity scores (%) for drug names (orthographic, phonetic, combined).
  - Uses some letter strings as approximate matches (oc vs. or, ra vs. la, iv vs. in, an vs. as). These strings are based on analysis of name confusion errors.
  - Orthographic score is a composite of two measures (BISIM and edit distance). The two are normalized to generate two scores between 0 and 1 and averaged to generate a match %.
  - ALINE algorithm used to calculate the phonetic score
  - COMBINED match is an average of phonetic and orthographic score for the name pair.

- Higher scores equate with greater similarity.

Rationale for Using POCA

- More scientific approach:
  - The POCA measures are objective
  - The COMBINED measure of similarity has been positively correlated to errors involving name confusion

- Publically available to download:

http://www.fda.gov/Drugs/ResourcesForYou/Industry/ucm400127.htm

- Automation of processes:
  - POCA search reduces manual database searching
  - Reproducible results: the measure of similarity for any given pair should be the same whether FDA or the Applicant performs the search* *(except for proposed names that are only available on FDA internal databases)*

Limitations of POCA

- Not designed to evaluate the influence of product characteristics
    - Product characteristics may increase or decrease the potential for confusion
- Not designed to evaluate or consider influence of other known causes of name confusion that could lead to errors
    - For example, metathesis leading to confusion between Zocor and Cozaar is unlikely to be evaluated using POCA approach (similarity scores <50%)
- However, additional processes are recommended to uncover sources of error that might not be detected using POCA:
    - Conduct name simulation studies
    - Conduct manual analysis of product characteristics

Role of Product Characteristics

- Product strength and dose is an important consideration
  - For similar names, the risk of medication error is potentiated when the strengths and doses overlap or are similar to one another.
  - However, if none of the strengths overlapped, the name similarity ***might*** not lead to errors.
- Other attributes such as indications, dosing frequencies and administration may contribute but with varying impact

Why Consider Product Characteristics

- Root Cause Analysis shows that **shared strength or dose** contribute to confusion and has lead to errors between drugs with similar names.
- Conversely, evaluation of post-marketing errors leads us to conclude that **differences in strength** may help to mitigate the risk of confusion.
  - Consider: Intuniv and Invega 3 mg strengths **have** been confused
  - Intuniv 1 mg, 2 mg, and 4 mg and Invega 1.5 mg, 6 mg, and 9 mg product strengths **have not** been confused.
- Other attributes such as indications, dosing frequencies and administration may contribute but with varying impact

Limitations of Product Characteristics

- Different product characteristics may not prevent confusion between highly similar drugs names

- Confusion has occurred even when products have very different doses, therapeutic uses, dosage forms, route of administration, and setting of use. Consider these errors:
  - Cerebyx (an injectable anti-convulsant drug) and Celebrex (an oral NSAID) (combined POCA score of 74%).
  - Advair (an inhalation product) and Advicor (a tablet) (combined POCA score of 70%)
  - Durasal (a topical wart remover) and Durezol (an ophthalmic drop) (combined POCA score of 78%).

- **If two products have highly similar names, differences in the product profile may not reduce the risk of error.**

Analyzing POCA Results

POCA Results: Analyze

1. Group the name pairs into one of the following three categories
   - Highly Similar Pair: combined match percentage score ≥70%.
   - Moderately Similar Pair: combined match percentage score ≥50% to ≤ 69%; and any names identified in the simulation studies that have combined scores ≤49%.
   - Low Similarity: combined match percentage score ≤49%.
2. Use checklists to determine if confusion and error would occur
   - Developed for each category using the principles of Failure Modes and Effects Analysis
   - Provided for each category in Appendices of Guidance

Highly Similar Names (>70%)

- Differences in product characteristics may not prevent the risk of a medication error
- Checklist focuses on first whether the names themselves have sufficient differences in appearance and sound to avoid to confusion
- If names are viewed as sufficiently different, then consider the influence of product characteristics on the potential for confusion (i.e. Consult the moderately similar checklist)

Moderately Similar Pairs (i.e., combined score is ≥50% to ≤69%)

- Focus is on the role of product characteristics in increasing or decreasing the potential for confusion.
- Determine if strengths and doses of the name pair overlap or are very similar.
    - Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion
- Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion.
    - Evaluate these pairs further to determine if the pattern of orthographic or phonetic differences in the names would prevent confusion

Low Similarity Pairs (≤49%)

- In most circumstances, these names are viewed as sufficiently different to minimize confusion.
- Exceptions might occur where there are data from simulation studies that suggest that the name is susceptible to misinterpretation as marketed product name.
  - In such instances, we recommend that you reassign a low similarity name to the moderate similarity category and review accordingly.

Checklists: Results

- If you find that the name is likely to result in error due to similarity and/or shared product characteristics, this is likely to be a concern identified in FDA's look and sound-alike safety assessment.

V. Final Determination on Name Acceptability

V Final Determination

- The acceptability of a proposed proprietary name is based on FDA's review of all information and analyses described in the guidance (i.e. Sections I-IV), along with any information submitted by the Applicant).
- FDA may reject a name if, based on the information provided or in its own review, it determines the name:
  - causes confusion with other products that can result in medication errors and preventable harm or
  - is misleading with respect to the therapeutic effectiveness, composition, or the safety of the product.

For further questions please contact

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Q & A Session